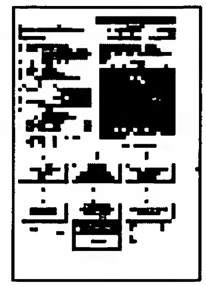
The Delphion Integrated View

Title: **JP07224081A2: PRODUCTION OF DEOXYRIBOFURANOSYL HALIDE DERIVATIVE**

Derwent Title: 2-Deoxy:ribofuranosyl halide derivs. prepn. - comprises reacting deoxy:ribofuranose derivs. with halogenating agent in alcohol [Derwent Record]

Country: JP Japan

Kind: A



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Published / Filed: **1995-08-22** / 1994-02-10

Application Number: **JP1994000016430**

IPC Code: Advanced: C07H 5/02;
Core: C07H 5/00;
IPC-7: C07H 5/02;

Priority Number: 1994-02-10 **JP1994000016430**

Abstract: PURPOSE: To obtain in an industrially advantageous way a deoxyribofuranosyl halide derivative useful as an intermediate for 2'-deoxynucleotides by reaction of a 2-deoxyribofuranose derivative with a halogenating agent in the presence of an alcohol or water.

CONSTITUTION: A 2-deoxyribofuranose derivative of formula I (R1 is an alkyl; R2 and R3 each is a protecting group) [e.g. 3,5-bis (p-chlorobenzoyl)-2-deoxy-1- methylribofuranose] and a halogenating agent (e.g. acetyl chloride) are dissolved in a solvent such as cyclohexane followed by adding an alcohol (e.g. methanol) or water to the resultant solution to carry out chlorination at 25°C for 4 hr under agitation; volatiles are then distilled off at reduced pressures from the reaction mixture, and the resultant mixture is incorporated with cyclohexane followed by agitation for 2 hr under chilling with ice, and the crystal deposited is subjected to filtration, washed and then dried, thus safely and efficiently obtaining the aimed deoxyribofuranosyl halide derivative of formula II (X is a halogen).

Family: None

7-224081

[Title of the Invention]

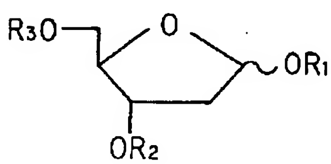
PRODUCTION METHOD OF DEOXYRIBOFURANOSYL HALIDE

[Abstract]

[Constitution]

A 2-deoxyribofuranose derivative defined by the following formula [I]:

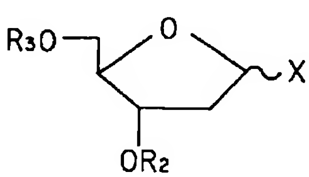
[Kagaku 6]



-----[I]

wherein R_1 denotes an alkyl and R_2 and R_3 respectively denote a same or different protection group: is reacted with a halogenation agent in the presence of alcohol or water to obtain a 2-deoxyribofuranosyl halide derivative defined by the following formula [II]:

[Kagaku 7]



-----[II]

wherein R_2 and R_3 respectively denote a same or different protection group and X denotes a halogen.

[Effect]

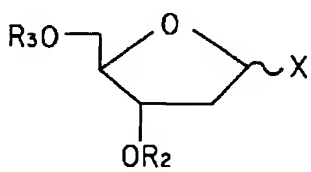
The 2-deoxyribofuranosyl halide derivative is safely and efficiently obtained.

[Claims]

[Claim 1]

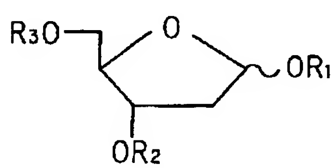
A production method of a 2-deoxyribofuranosyl halide derivative defined by the following formula [II]:

[Kagaku 2]


-----[II]

wherein R_2 and R_3 respectively denote a same or different protection group and X denotes a halogen: by reaction of 2-deoxyribofuranose derivative defined by the following formula [I]:

[Kagaku 1]


-----[I]

wherein R_1 denotes an alkyl and R_2 and R_3 respectively denote a same or different protection group: with a halogenation agent in the presence of alcohol or water.

[Claim 2]

The production method of a 2-deoxyribofuranosyl halide derivative according to claim 1, wherein R_1 denotes a lower alkyl having 1 to 4 carbon atoms.

[Claim 3]

The production method of a 2-deoxyribofuranosyl halide

derivative according to claim 2, wherein R_1 denotes methyl.

[Claim 4]

The production method of a 2-deoxyribofuranosyl halide derivative according to claim 1, wherein R_2 and R_3 respectively denote an acyl.

[Claim 5]

The production method of a 2-deoxyribofuranosyl halide derivative according to claim 4, wherein R_2 and R_3 respectively denote an aromatic acyl.

[Claim 6]

The production method of a 2-deoxyribofuranosyl halide derivative according to claim 4, wherein the alcohol is a lower alcohol having 1 to 4 carbon atoms.

[Claim 7]

The production method of a 2-deoxyribofuranosyl halide derivative according to claim 6, wherein the alcohol is methanol.

[Detailed Description of the Invention]

[0001]

[Industrial Field of the Invention]

The invention relates to a production method of a 2-deoxyribofuranosyl halide derivative useful as an intermediate of 2-deoxynucleosides.

[0002]

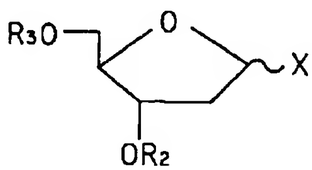
[Prior Art]

Conventionally, the following production methods have

been known as a common production method of 2-deoxyribofuranosyl halide derivative defined by the following formula [II].

[0003]

[Kagaku 3]



-----[II]

[0004]

wherein R_2 and R_3 respectively denote a same or different protection group and X denotes a halogen.

(1) A method of reaction of 3,5-bis(p-chlorobenzoyl)-2-deoxy-1-methylribofuranose with dried hydrogen chloride in acetic acid (J. Org. Chem., 34, 3806 (1969)) and

(2) a method of treatment of 3,5-diacyl-2-deoxy-1-methylribofuranose with acetyl halide in acetic acid (reference to Japanese Patent Application Laid-Open (JP-A) No. 62-12790). However, these methods inevitably use high concentration hydrogen chloride gas or a large quantity of acid halide compounds, and therefore there has been a problem in working environments that acidic gas or mist of the acid halide compounds is diffused.

[0005]

Also, in the case of synthesizing a relatively large quantity of a halide derivative (Kagaku 3) (e.g., in the case

of synthesis in industrial scale), it is difficult to avoid the danger of the above-mentioned large quantity of acidic gas or acid halide compounds.

[0006]

[Problems to be Solved by the Invention]

The purpose of the invention is to provide a production method for safely and efficiently obtaining 2-deoxyribofuranosyl halide derivative (kagaku 3).

[0007]

[Means for Solving the Problems]

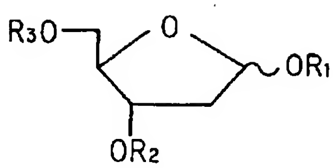
The inventors of the invention have made various investigations and accordingly have found that 2-deoxyribofuranose derivative of which hydroxyl groups at third and fifth positions is efficiently reacted with a halogenation agent in the presence of an alcohol or water.

[0008]

The production method of 2-deoxyribofuranosyl halide derivative of the invention has been accomplished based on the above-mentioned finding and more particularly the method is characterized in that 2-deoxyribofuranose derivative defined by the following formula [I]:

[0009]

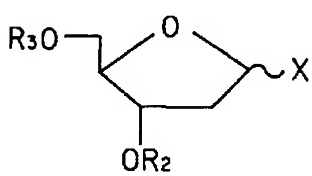
[Kagaku 4]

 ------[I]

[0010]

wherein R_1 denotes an alkyl and R_2 and R_3 respectively denote a same or different protection group: is reacted with a halogenation agent in the presence of alcohol or water to obtain a 2-deoxyribofuranosyl halide derivative defined by the following formula [II]:

[Kagaku 5]

 -----[II]

[0012]

wherein R_2 and R_3 respectively denote a same or different protection group and X denotes a halogen. Hereinafter, the invention will be described more in detail.

[0013]

(Starting substance)

In the 2-deoxyribofuranose derivative (a starting substance) defined by the above-mentioned formula [I], R_1 denotes an alkyl and in terms of the solubility in an organic material (e.g., a halogenation agent and a solvent), R_1 is preferable to denote a lower alkyl having 1 to 4 carbon atoms (e.g., methyl).

[0014]

R_2 and R_3 may denote a same or different protection groups and in terms of the easiness of the synthesis of the starting substance, R_2 and R_3 denote a same group.

[0015]

For R^2 and R^3, groups commonly used for protection groups in fields of sugar chemistry may be used without particular limit if they are protection groups inactive to the halogenation reaction to be employed in the invention. For example, an alkyl (preferably a lower alkyl having 1 to 4 carbon atoms), a cycloalkyl, an aryl (preferably an aryl having 6 to 20 carbon atoms), an aralkyl (preferably an aralkyl having 7 to 20 carbon atoms such as benzyl), an acyl, a silanyl, a silyl, a furanyl, and a pyranyl may be used for R^2 and R^3.

[0016]

The above-mentioned acyl may include both of an aliphatic acyl (preferably an aliphatic acyl having 1 to 10 carbon atoms) and an aromatic acyl (preferably an aromatic acyl having 7 to 20 carbon atoms) and in terms of the stability, handling property, and crystallinity at the time of halogenation reaction, an aromatic acyl is preferable to be used. These acyl groups may have one or more substituent groups such as a halogen, an alkyloxy, a nitro, an acyl, an alkyl (in the case of aromatic acyl) based on the necessity. More particularly, the above-mentioned acyl includes substituted or unsubstituted aliphatic acyl such as acetyl and propionyl; and aromatic acyl such as benzoyl, toluoyl,

nitrobenzoyl, p-chlorobenzoyl, methoxybenzoyl, and m-chlorobenzoyl.

[0017]

A method for obtaining the above-mentioned starting substance to be used in the invention is not particularly limited. For example, the starting substance (in the case R_2 and R_3 denote acyl) is obtained by treating deoxyribose with hydrochloric acid (or sulfuric acid)-methanol for conversion into methyldeoxyriboside and causing reaction of methyldeoxyriboside with an acyl halide in pyridine for acylation of hydroxyl.

[0018]

(Halogenation agent)

Acid halides, halogenated silyl compounds, and inorganic halides may be used as the halogenation agent and in terms of the handing property (easiness for removal), acid halides are preferable to be used. More practically, acid halides of fatty acids such as acetyl chloride, acetyl bromide, propionyl chloride, and propionyl bromide; halogenated silyl compounds such as trimethylchlorosilane; and inorganic halides such as thionyl chloride, SO_2Cl_2, and $TiCl_4$ may be used preferably.

[0019]

In the invention, it is preferable to use generally 1 to 10 mole (preferably 2 to 4 mole) of the halide to 1 mole of the starting substance defined by the formula [I]. If the number

of the mole of the halide is small, the reaction is slow and if the number of the mole is too high, the reagent is consumed in vain.

[0020]

(Alcohol)

As the alcohol, both of aliphatic alcohols (preferably lower alcohols having 1 to 4 carbon atoms) and aromatic alcohols (preferably alcohols having 6 to 20 carbon atoms) are usable if the alcohols contain hydrogen atom (active hydrogen) active enough to produce hydrogen chloride by reaction with the above-mentioned halogenation agent. The number of hydroxyl groups in the alcohol is not particularly limited, however mono-, di-, or tri-hydric alcohols are preferable to be used. In terms of the solubility of the starting substance and the boiling point of the alcohol, monohydric alcohols are particularly preferable to be used. In terms of the post-treatment after the halogenation reaction, the boiling point of the alcohol is preferably about 60 to 120°C.

[0021]

More particular examples to be used as the above-mentioned alcohol are monohydric alcohols such as methanol and ethanol; and polyhydric alcohols such as ethylene glycol, propylene glycol, and glycerin.

[0022]

The above-mentioned alcohol (or water) may be used at a

ratio generally 0.05 to 1 mole, preferably 0.08 to 1 mole (particularly preferably 0.12 to 0.7 mole) to 1 mole of the above-mentioned halogenation agent

[0023]

(Halogenation reaction)

In the invention, halogenation of the starting substance is carried out by reaction of the starting substance (2-deoxyribofuranose derivative) with the above-mentioned halogenation agent in the presence of an alcohol or water.

[0024]

The above-mentioned halogenation reaction may be carried out while using the above-mentioned halogenation agent in place of a solvent or in combination with a proper solvent. From a viewpoint of the easiness of the post-treatment and cost, it is preferable to use a solvent.

[0025]

Type of the above-mentioned solvent is not particularly limited if it does not inhibit the halogenation reaction (that is, practically inactive to the above-mentioned halogenation). More particular examples of the solvent are aliphatic and aromatic hydrocarbons such as hexane, cyclohexane, benzene, and toluene; aliphatic and aromatic halogenated hydrocarbon such as methylene chloride, dichloroethane, chloroform, isopropyl bromide (i-PrBr), n-butyl chloride (n-BuCl), amyl chloride (n-AmCl), and chlorobenzene; ethers such as dimethyl ether and

diethyl ether; esters such as methyl acetate and ethyl acetate; ketones such as acetone, methyl ethyl ketone, and methyl isobutyl ketone; and organic acids such as acetic acid. These solvents may be mixed properly for the use if necessary. In terms of the post-treatment after the halogenation reaction, the boiling point of the above-mentioned solvent is preferable about 30 to 120°C.

[0026]

The use amount of the solvent is not particularly limited, however in terms of the reaction efficiency and the post-treatment easiness, it is preferably about 2 to 20 ml (more preferably about 5 to 16 ml) in the case the amount of the starting substance is 36.7 mmol.

[0027]

(Reaction condition)

The reaction temperature may properly be selected depending on the halogenation agent and the solvent, however in general it is preferably -30°C to 50°C (more preferably -10°C to 30°C).

[0028]

The reaction time may properly be selected depending on the halogenation agent, the solvent, the mole ratio of the respective components, and the reaction temperature, however in general it is preferably about 15 minutes to 20 hours (more preferably about 30 minutes to 5 hours).

[0029]

After the above-mentioned halogenation reaction, proper post-treatment to the reaction product is carried out to obtain an aimed product (2-deoxyribofuranosyl halide derivative defined by the above-mentioned formula [II]). More practically, for example, a volatile substance (excess halogenation agent, solvent, and the like) are removed from the reaction product by reduced pressure distillation and the residue is refined by chromatography or precipitated in a proper solvent and then produce solid matter is separated by filtration and dried to obtain the aimed compound.

[0030]

Herein, any solvent may be used without any particular limit as a solvent to be used for obtaining the aimed compound [II] if it neither react on nor dissolve the aimed compound [II]. Solvents may be mixed properly and used if necessary.

[0031]

The 2-deoxyribofuranosyl halide derivative [II] obtained in the above-mentioned manner may be used as it is for the next reaction, however it may be refined by recrystallization or the like based on the necessity.

[0032]

Hereinafter, the invention will be described more in detail with reference to examples, however it is not intended that the invention be limited to the illustrated examples.

[0033]

[Examples]

Example 1

3,5-bis(p-chlorobenzoyl)-2-deoxy-1-methylribofuranose (R_1 = methyl; R_2 = R_3 = p-chlorobenzoyl in the formula [I]) (0.0367 mol) and acetyl chloride (halogenation agent) 10 gr (0.127 mol) were dissolved in cyclohexane (solvent I) 8 ml and methanol 1.5 ml was added to the mixture. The obtained solution was stirred at 25°C for 4 hours to carry out chlorination reaction. Next, volatile substance was removed from the reaction mixture by reduced pressure distillation and cyclohexane (solvent II) 16 ml was added to the reaction mixture and stirred for 2 hours under ice cooling condition. The precipitated crystal was separated by filtration and washed with a small amount of cyclohexane and dried to obtain 3,5-bis(p-chlorobenzoyl)-2-deoxyribofuranosyl chloride (R_2 = R_3 = p-chlorobenzoyl in the formula [II]) 13.4 gr (yield 84.8%).

[0034]

The product obtained in the above-mentioned manner showed the following physical properties.

[0035]

Melting point: 121 to 122°C

^{1}H-NMR ($CDCl_3$): δ 2.7 to 2.9 (m, 2H)

4.6 to 4.7 (m, 2H)

4.7 to 4.9 (m, 1H)

5.5 to 5.6 (m, 1H)

6.4 to 6.5 (d, 1H)

7.4 to 7.5 (m, 4H)

7.9 to 8.1 (m, 4H)

Example 2

3,5-bis(p-chlorobenzoyl)-2-deoxy-1-methylribofuranose was chlorinated to obtain 3,5-bis(p-chlorobenzoyl)-2-deoxyribofuranosyl chloride in the same manner as Example 1, except that 1,2-dichlrooethane (DCE), acetone, cyclohexane, methyl isobutyl ketone (MIBK), or n-butylchloride (n-BuCl) was used as the above solvent I (reaction solvent) and cyclohexane, MIBK, acetone, or n-BuCl was used as the above solvent II and the reaction conditions described in the following Table 1 were employed.

[0036]

The obtained results are shown in the following Table 1 and Table 2.

[0037]

[Table 1]

Chlorination in AcCl-Solvent I-Methanol System

No.	AcCl to 2DR	Solvent I	MeOH to AcCl	Reaction temperature, time	solvent II	Yield	Remark
1	2 times as much (by mole)	DCE 16 ml	1/3 times as much (by mole)	25°C 2 hrs	Cyclohexane 16 ml	67.8%	
2	2 times as much (by mole)	DCE 16 ml	1/12 times as much (by mole)	25°C 9 hrs	Cyclohexane 16 ml	67.8%	
3	2 times	DCE	1/2 times	25°C	Cyclohexane	71.6%	

	as much (by mole)	16 ml	as much (by mole)	4 hrs	16 ml		
4	2 times as much (by mole)	DCE 16 ml	1/2 times as much (by mole)	35°C 4 hrs	Cyclohexane 16 ml	65.9%	*1
5	3 times as much (by mole)	DCE 32 ml	1/3 times as much (by mole)	25°C 4 hrs	Cyclohexane 16 ml	75.4%	
6	4 times as much (by mole)	Acetone 32 ml	1/6 times as much (by mole)	25°C 6 hrs	Cyclohexane 24 ml	71%	
7	3 times as much (by mole)	DCE 32 ml	1/3 times as much (by mole)	25°C 3 hrs	Cyclohexane 24 ml	78.3%	
8	3 times as much (by mole)	DCE 32 ml	1/2 times as much (by mole)	25°C 4 hrs	Cyclohexane 24 ml	77.7%	
9	3 times as much (by mole)	DCE 32 ml	1/3 times as much (by mole)	10°C 4 hrs	Cyclohexane 25 ml	79.2%	
10	3 times as much (by mole)	DCE 32 ml	1/3 times as much (by mole)	5°C 4 hrs	Cyclohexane 30 ml	81.7%	
11	3 times as much (by mole)	DCE 16 ml	1/3 times as much (by mole)	5°C 4 hrs	Cyclohexane 30 ml	55.1%	*2

[0038]

[Table 2]

No.	AcCl to 2DR	Solvent I	MeOH to AcCl	Reaction temperature , time	solvent II	Yield	Remark
12	3 times as much (by mole)	Cyclohexane 16 ml	1/3 times as much (by mole)	10°C 4 hrs	Cyclohexane 30 ml	82.3%	
13	3 times as much (by mole)	Cyclohexane 16 ml	1/3 times as much (by mole)	20°C 4 hrs	Cyclohexane 30 ml	84.2%	
14	3 times as much (by mole)	Cyclohexane 16 ml	1/3 times as much (by mole)	10°C 4 hrs	Cyclohexane 30 ml	83.5%	*3
15	3 times as much (by mole)	Cyclohexane 16 ml	1/3 times as much (by mole)	25°C 4 hrs	Cyclohexane 35 ml	84.8%	$\alpha/\beta \cong$ 15/85
16	3 times as much (by mole)	MIBK 16 ml	1/3 times as much (by mole)	5°C 4 hrs	MIBK 5 ml	82.3%	$\alpha/\beta =$ 43/95.7
17	3 times as much	Acetone 16 ml	1/3 times as	5°C 4 hrs	Acetone 5 ml	81.0%	

	(by mole)		much (by mole)				
18	3 times as much (by mole)	n-Bu•Cl 10 ml	1/3 times as much (by mole)	25°C 4 hrs	n-Bu•Cl 16 ml	79.2%	α/β = 7/93
19	3 times as much (by mole)	Cyclohexane 8 ml	1/3 times as much (by mole)	25°C 4 hrs	n-Bu•Cl 16 ml	80.4%	
20	3 times as much (by mole)	Cyclohexane 8 ml	1/3 times as much (by mole)	25°C 4 hrs	n-Bu•Cl 20 ml	80.0%	
21	3.3 times as much (by mole)	Cyclohexane 8 ml	1/3 times as much (by mole)	25°C 4 hrs	n-Bu•Cl 20 ml	81.7%	α/β = 5/95

[0039]

*1: The yield was decreased if the reaction temperature was high.

[0040]

*2: After the solvent was removed by distillation and it was kept at 50°C, the crystal was filtered.

[0041]

*3: After the solvent was removed by distillation and it was kept at 45°C in cyclohexane for 5 hours, the crystal was filtered.

[0042]

"2DR" shown in the above Table 1 and Table 2 denotes 3,5-bis(p-chlorobenzoyl)-2-deoxy-1-methylribofuranose, "MeOH" denotes methanol, and "AcCL" denotes acetyl chloride.

[0043]

The ratio α/β shown in the above Table 1 and Table 2 was calculated from the peak surface area ratio of HPLC chromatogram

obtained by analysis of HPLC of α- and β-thymidine derivatives after the chloro group at the first position of the produced 3,5-bis(p-chlorobenzoyl)-2-deoxyribofuranosyl chloride was reacted with silyled thymine for conversion into the α- and β-thymidine derivatives.

[0044]

As described above-mentioned, as the reaction solvent, DCE, acetone, cyclohexane, MIBK, or n-BuCl was used and in the case DCE or n-BuCl was used, the stability of the obtained Cl-body at 35°C was slightly low as compared with that in the case using other solvents (however, sufficient stability was observed in the case of small scale reaction).

[0045]

In the case acetone or MIBK was used, the apparent yield was approximately same, however proceeding of chlorination reaction was slightly slow and the purity of the aimed product was also slightly low.

[0046]

On the other hand, in the case cyclohexane was used as the reaction solvent, the reaction proceeding speed was proper and the Cl-body was stable even at 50°C.

[0047]

Example 3

3,5-bis(p-chlorobenzoyl)-2-deoxy-1-methylribofuranose was chlorinated to obtain

3,5-bis(p-chlorobenzoyl)-2-deoxyribofuranosyl chloride in the same manner as Example 1, except that 2DR, the starting substance, 4.93 g (36.7 mmol) was used; $SOCl_2$ was used as a halogenation agent; acetic acid (AcOH) was used as the reaction solvent; and the reaction conditions described in the following Table 1 were employed.

[0048]

The obtained results are shown in the following Table 3.

[0049]

[Table 3]

Chlorination by $SOCl_2$

exp.	$SOCl_2$	AcOH	Temperature	Time	Yield	Remark
1	9 gr. (2.06 times as much)	16 ml	5°C	1 hr	12.6 gr. (79.8%)	
2	9 gr. (2.06 times as much)	16 ml	5°C	2 hrs	12.2 gr. (76.6%)	
3	9 gr. (2.06 times as much)	16 ml	5°C	2 hrs	11.8 gr. (74.7%)	*4
4	6.6 gr. (1.5 times as much)	16 ml	5°C	2 hrs	11.8 gr. (74.7%)	
5	5.3 gr. (1.2 times as much)	16 ml	5°C	2 hrs	12.0 gr. (75.9%)	
6	21.9 gr.	-	10°C	Over night	8.1 gr. (51.3%)	
7	6.6 gr. (1.5 times as much)	16 ml	15°C	2 hrs	11.9 gr. (75.4%)	
8	6.6 gr. (1.5 times as much)	16 ml	5°C	5 hrs	12.2 gr. (77.3%)	
9	21.9 gr.	-	5°C	2 hrs	0.3 gr.	*4
10	13.2 gr. (3 times as much)	-	5°C	Over night	5.8 gr. (36.7%)	*4
11	6.6 gr. (1.5 times as much)	16 ml	25°C	2 hrs	12.1 gr. (76.6%)	
12	5.3 gr. (1.2 times as much)	16 ml	5°C	5 hrs	12.3 gr. (77.9%)	
13	5.3 gr. (1.2 times as much)	16 ml	25°C	2 hrs	12.7 gr. wet	

[0050]

*4: While $SOCl_2$ was removed by distillation, halogenation reaction was carried out.

[0051]

<u>Example 4</u>

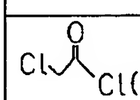
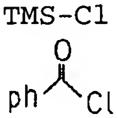
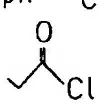
3,5-Bis(p-chlorobenzoyl)-2-deoxy-1-methylribofuranose was chlorinated to obtain 3,5-bis(p-chlorobenzoyl)-2-deoxyribofuranosyl chloride in the same manner as Example 1, except that 2DR, the starting substance, 4.93 g was used; acetic acid (AcOH) was used as the reaction solvent; and the reaction conditions described in the following Table 1 were employed.

[0052]

The obtained results are shown in the following Table 4.

[0053]

[Table 4]

Chlorination agent (75.6 mmol)		Reaction condition	Starting of crystal precipitation	Yield
 (CAC)	, 8.5 g	25°C, 19 hr	4.5 hr	8.4 g (53.2%)
TMS-Cl	, 8.2 g	25°C, 19 hr	1 h 40 min	9.8 g (62.1%)
	, 10.6 g	25°C, 30 hr	Over night	4.6 g (29.1%)
	, 7.0 g	25°C, 4 hr		10.2 g (64.6%)
SO_2CL_2	, 9.0 g	25°C, 40 min	5 to 10 minutes	12.2 g (77.3%)

[0054]

[Effect of the Invention]

As described, according to the invention, a production method capable safely and efficiently obtaining 2-deoxyribofuranosyl halide derivative is provided.